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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,995	07/25/2002	Marinus Gerardus Cornelis Kivits	2001-1028	5816

466 7590 02/26/2007

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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,995	KIVITS ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The amendment received 30 November 2006 in response to the Office Action of 30 June 2006 has been entered. Claims 1-15 have been cancelled. New claims 16-35 have been presented and made of record. Claims 16-35 are pending in the instant application.

Withdrawn Objections

The objection to the IDS filed 8 April 2002 as not in compliance with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 is withdrawn in view of applicants submission of Reference JP 00279312. This reference has now been considered and so indicated on the signed the IDS submitted on 30 November.

Maintained/New Grounds for Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-32 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25(a) recites "eluting the cationic exchange resin column with a salt solution at a concentration of a 0.3-0.5M and a .....". It is not clear if applicant intends to recite a specific salt, i.e. a 0.3-0.5M NaCl solution or recite a salt concentration of 0.3-0.5M or something else entirely.

Claims 26-32 are included in this rejection as being dependent from a rejected claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-35 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record and for reasons set forth below, because the specification, while being enabling for a process for extracting TGF-β and IGF-1 and lactoperoxidase from a milk product comprising the steps of:

a. eluting a basic fraction from a cationic exchange resin with a 0.24M NaCl solution, pH of about 6.5 or a 0.28 M NaCl/10mM ammoniumacetate solution, pH 5.5

b. passing the basic fraction (from step a) over a hydroxyapatite column

c. eluting the hydroxyapatite column sequentially with at least two eluents, said eluents comprising phosphate buffers of increasing salt concentrations wherein the first eluent has a sodium phosphate concentration of 0.05 to 0.2 M and a pH of about 6 and the second eluent has a sodium phosphate concentration of 0.2 to 0.3M and a pH of about 6 or eluting the hydroxyapatite column with at least two eluents said eluents comprising a first eluent comprising 0.12M NaCl/25mM phosphate and a pH of about 7.0 and a second eluent comprising 0.35M NaCl/25mM phosphate and a pH of about 7.0

d. eluting the hydroxyapatite column with a third eluent wherein the eluent has a salt concentration of 0.3 to 0.5M and a pH of 7.0 or a third eluent wherein the eluent has a salt concentration of 1M NaCl/25mM phosphate and a pH of 7.0

thereby eluting, sequentially, fractions enriched for IGF-1, TGF-β, and lactoperoxidase

does not reasonably provide enablement for

a. eluting a basic fraction from a cation exchange column by utilizing any elution buffer or an elution buffer with a salt solution at a concentration of a 0.3M-0.5M salt and a pH between 5.5 and 7.5

b. eluting the hydroxyapatite column sequentially with at least two eluents of increasing pH concentrations

c. eluting the hydroxyapatite column with a third eluent, said third eluent being selected from any phosphate buffers, sodium chloride solutions and potassium chloride solutions

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants traverse this rejection as applied to previously presented claims 1-7. The reason for the traversal is that the prior art does not suggest that practicing the claimed invention would be an unpredictable endeavor or constitute an undue burden in view of the present disclosure.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The claims of the instant invention are all drawn to a process for extracting transforming growth factor β (TGF-β) and insulin-like growth factor 1 (IGF-1) from a milk product, the process resulting in fractions of specifically identified characteristics:

i. a fraction comprising IGF-1 wherein the ratio of IGF-1 to TGF-β is greater than 10:1

ii. a fraction comprising TGF-β to IGF-1 is greater than 5:1

The third fraction is identified as comprising lactoperoxidase.

While the art discloses methods of obtaining fractions highly enriched in growth factors, the claims of the instant invention recite a method of further obtaining fractions enriched for specific growth factors.

The specification teaches that after the adsorption of the desired components onto the cationic exchange resin, an elution step is carried out. The preferred elution solution is one comprising sodium chloride or potassium chloride buffered at pH 5.5 and

7.5. However, the specification does not provide guidance as to the range of salt concentration one would use in this step of the process. As previously stated (Office Action of 30 June 2006, page 7, 1st paragraph), the art teaches methods of eluting growth factor-rich fractions from milk by utilizing NaCl buffers at various salt concentrations. Thus, one of ordinary skill in the art could utilize only the guidance presented in the working examples 1-3, which recite eluting a basic fraction from a cationic exchange resin with a 0.24M NaCl solution, pH of about 6.5 or a 0.28 M NaCl/10mM ammoniumacetate solution, pH 5.5 to predictably obtain a fraction enriched in growth factors.

The claims recite as step c, eluting the hydroxyapatite column sequentially with at least two eluents of increasing pH. While the specification discloses that "It is also possible to apply an increasing pH gradient" (page 6, line 15), the working examples provide no guidance as to a method of eluting the hydroxyapatite column sequentially with eluents of increasing pH. A shift in pH from 5.5 to 7.0 represents a 50-fold decrease in hydrogen ion concentration. Thus, one of ordinary skill in the art could not predict that one would be able to obtain fractions of the specificity recited in the claims:

i. a fraction comprising IGF-1 wherein the ratio of IGF-1 to TGF-β is greater than 10:1

ii. a fraction comprising TGF-β to IGF-1 is greater than 5:1

by eluting the hydroxyapatite column sequentially with at least two eluents of increasing pH concentrations ranging from pH 5.5-7.

The claims broadly recite a third step of eluting the hydroxyapatite column with a third eluent having increased salt content or pH as compared to the first and second eluents, said third eluent selected fro the group consisting of phosphate buffers, NaCl solutions and KCl solutions to obtain a fraction comprising lactoperoxidase. The specification discloses eluting the hydroxyapatite column with a phosphate buffer having a pH of 5.5 to 8 and a phosphate concentration of 0.3 to 0.5M, preferably a pH of 7 and a phosphate concentration of 0.5M (page 6, lines 29-32). The working examples (Example 1, 2, and 4) teach elution of a native lactoperoxidase fraction with a high activity utilizing a buffer of 0.5M phosphate, pH 7.0 (Examples 1 and 2) or utilizing a

buffer of 1M NaCl/25 mM phosphate. Thus, one would not be able to predict that eluting a hydroxyapatite column with a third elution buffer comprising a buffer of increased salt content or pH as compared to the first and second eluents, said third elution buffer selected from any phosphate buffers, sodium chloride solutions and potassium chloride solutions would result in a third fraction comprising a lactoperoxidase fraction with a high activity.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Claim 24 recites "eluting said basic fraction with a salt solution buffered at a pH between 5.5-8". The specification (page 5, lines 25-27) disclose elution of components with a salt solution buffered at a pH between 5.5 and 7.5. Thus, the recitation of a salt solution buffered at a pH between 5.5 and 8 constitutes the introduction of new matter.

Conclusion:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS